Triglyceride clearance in subjects with heterozygous EXT1 or EXT2 Mutations

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON33207

Source
ToetsingOnline

Brief title
TEAM

Condition

- Other condition

Synonym
Hereditary Multiple Exostosis, Multiple Osteochondroma

Health condition

hypertriglyceridemie

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: heparan sulfate, Triglycerides

Outcome measures

Primary outcome

Triglyceride clearance

Secondary outcome

LPL binding capacity

Urine albumin and glycosaminoglycan profile

Study description

Background summary

Hypertriglyceridemia is an independent risk factor for cardiovascular disease and can be caused by decreased clearance of triglyceride-rich lipoproteins(TRLs) in the liver. In this protocol we will focus on a recently discovered pathway in which TRLs are cleared through heparan sulfate proteoglycans (HSPGs)-assisted endocytosis in the liver. Animal research has elucidated many of the steps in this process but human relevance still remains to be determined. Our hypothesis is that HSPGs are instrumental in the removal of TRLs from the circulation in humans. An important gene in this process, EXT codes for exostosin, which is involved in the elongation of heparan sulphate, a glycosaminoglycan present throughout the human body. Patients with EXT-1 and EXT-2 mutations have a defect in their heparin sulfate synthesis and could therefore help elucidate the role of HSPGs in triglyceride clearance. The patients are characterized by the HMO (hereditary multiple osteochondroma) syndrome; they develop multipe benign epiphysial bone tumors during (pre-) puberty due to 50% reduction in heparansulfate synthesis. Further assessment of their metabolism has thus far never been published. Knowing that heparin sulfate in mice are important in triglyceride metabolism, we are interested whether human subjects with mutations in the gene coding for HS are also characterized by impaired triglyceride clearance. We will therefore ask

patients with HME/MO to participate in an Oral Fat Loading Test (OFLT) combined with an LPL test (Lipoprotein Lipase) to elucidate the human relevance of heparan sulfate in triglyceride metabolism.

Study objective

In the current study we want to evaluate the triglyceride clearance in a population with EXT-1 and EXT-2 mutations (n=15) and their unaffected family members (n=15). We will perform:

* Oral fat loading test (OFLT) to investigate lipid clearance
* LPL test to determine LPL binding
* Standard CV risk biochemistry panel(incl. Cholesterol/crp/hba1c). Also plasma/urine samples for determination of total glycosaminoglycan concentration, hyaluronan with degrading enzyme hyaluronidase, heparin sulfate with degrading enzyme heparanase.

Subjects will be recruited from department of Orthopedics, OLVGC which is a national referral center for hereditary multiple osteochondromas. All studies/measurements will be performed at the AMC.

Study design

This is a pilot case control study, in which we will invite 15 subjects with a known EXT-1 or EXT-2 mutation and their unaffected family members to participate in this study. We will perform all measurements on one day. In the morning, after an overnight fast subjects will visit the AMC. There, a catheter will be inserted in the cubital vein and blood will be drawn. Moreover, patients will be asked to collect a morning urine sample for further analyses. Then, the Fat Loading Test will be initiated and subsequent hourly blood drawing is performed from a venous catheter. Finally, 8 hours after the start of the OFLT a bolus of heparin is infused (LPL test) and blood is drawn after 2, 5 10 and 15 min. Hereafter, the catheter will be removed and subjects are discharged.

Intervention

1. Fat loading test with subsequent blooddrawing
2. LPL-test using heparin

Study burden and risks

Fat loading test is a routine test in our department which requires repetitive blood sampling from an indwelling venous catheter after the consumption of cream and Vitamin A. The low dose of heparin used for the LPL test will not cause any side effects. We believe the information gathered from this study

outweighs the burden of these interventions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

HME/MO or familyrelatedness to HME/MO

Exclusion criteria

diabetes

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2009
Enrollment:	30
Type:	Anticipated

Ethics review

Approved WMO

Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL29065.018.09